MEDICAL STAFF CONFERENCE

Reactive Hypoglycemia

Mechanisms and Management

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. SLEISENGER:* Grand Rounds today involves an interesting disorder of carbohydrate homeostasis—hypoglycemia. The patient with this syndrome will be presented by Dr. Norman Coleman.

DR. COLEMAN:† A 26-year-old Caucasian woman was admitted to the hospital with a six-year history of headaches which had increased in frequency over the nine months before admission. Although they lasted several days each time, the headaches were never severe enough to cause her to stay home from work. They commenced in the neck, progressed to the side of the head and were not relieved by aspirin. Associated symptoms included sleepiness, slurred speech, chills, tremulousness, occasional diaphoresis and nausea, but no vomiting. The symptoms were unrelated to menses. There was no history of scotomata, loss of consciousness, seizures or other neurological symptoms during these episodes. There was no clear relationship to meals, although food did help the headaches. Past medical history included some nervousness which had been treated with chlordiazepoxide hydrochloride (Librium®). The patient had been taking norethindrane with mestranol (Orthonovum®) birth control pills for the past year. A 32-year-old sister had a history of headaches and hypoglycemia documented by glucose tolerance test. There was no known family history of diabetes.

Results of physical examination, including neurological testing, were entirely within normal limits. The blood pressure was 120/70 mm of mercury and the pulse regular at 76 beats per minute. Hemoglobin was 12.4 grams per 100 ml and leukocytes numbered 4,900 per cu mm with normal differential. Results of urinalysis, electrocardiogram, x-ray films of chest and skull, and an electroencephalogram were all within normal limits. A 24-hour urine measurement of 17-hydroxy- and 17-ketosteroid excretion was normal. A morning plasma cortisol level was 44 micrograms per 100 ml, while an early afternoon level the same day was 17 micrograms per 100 ml. Dexamethasone (2 mg) was administered at 11 p.m. the same day, and the plasma cortisol level was 4.5 mg per 100 ml on the following morning. The elevated plasma cortisol was considered compatible with the history of oral contraceptive therapy, since the pituitary-adrenal axis showed normal suppression. The oral glucose tolerance test showed the following results:

Time (hours)	0	½	1	1½	2	3	4	5
Plasma glucose (mg per 100 ml)	92	200	210	140	100	52	70	75

At the third and fourth hour periods of the glu-

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cose tolerance test the patient complained of headache similar to that she had experienced in the past. Reactive hypoglycemia was diagnosed and the patient was discharged with prescription of a high protein, low carbohydrate diet. On this dietary regime she has been asymptomatic for the two months since discharge from the hospital.

DR. SLEISENGER: This patient with hypoglycemia presents a difficult problem in diagnosis and treatment. Dr. John Karam will discuss some of these aspects.

DR. KARAM:* Patients who have rather nonspecific complaints and no abnormalities on physical examination are always a difficult management problem. A succession of normal laboratory tests usually confirms the initial impression that organic disease is not present, and the symptoms are then attributed to the tensions of modern living. Usually the only form of therapy given is reassurance, and since it does not often succeed the patient often consults a number of physicians and tries a succession of tranquilizers without benefit. Inevitably the question of hypoglycemia is raised, frequently by the patients themselves owing to wide publicity in the lay press. "Health food" store shelves are lined with current books paraphrasing the original classic, *Body, Mind, and Sugar*,[1] which emphasizes an almost mystical role of low blood sugar in many of the physical ills of our times. This book, written in 1951 and unrevised since the original publication, has been reprinted almost every year and remains a best seller. The authors of this book are a physician, E. M. Abrahamson, and one of his patients, A. W. Pezet, who had multiple complaints including nervousness, weakness, and fatigue which persisted despite attempts at management by numerous physicians. It was only after Dr. Abrahamson performed a glucose tolerance test and demonstrated a reduced blood sugar at three to four hours that successful therapy was begun. This therapy consisted of frequent, small feedings of a low carbohydrate, high protein diet. With the help of his patient, who was a professional journalist, Dr. Abrahamson wrote a very entertaining and expressive story of the dramatic results obtained in this and other cases.

The first half of the book gave an excellent and remarkably accurate scientific description of carbohydrate homeostasis with emphasis on the role of insulin in its regulation and the hazards of hyperinsulinism. While most readers in the scientific community would accept that Mr. Pezet's weakness, nervousness and fatigue could have been explained by the reactive hypoglycemia, it was more difficult to accept the second half of the book wherein the cure of his asthma, hay fever and allergies, as well as the cure of peptic ulcers, rheumatic fever and arthritis in other patients, was attributed to stabilization of the blood sugar level. Nevertheless, the book remains quite popular, despite its shortcomings, and a foundation located in New York distributes it nationally to its members who suffer in common from hypoglycemia.

In the patient presented today the obvious question is whether the headaches, nervousness and other nonspecific symptoms had any correlation with the documented measurement of a plasma sugar level of 52 mg per 100 ml recorded three hours after 100 grams of glucose was administered orally. Many physicians do not consider a blood glucose level above 40 mg per 100 ml or a plasma glucose above 46 mg per 100 ml to be low enough to cause hypoglycemic symptoms. In one study, continuous automatic monitoring of blood glucose demonstrated that nine out of twelve asymptomatic subjects had a blood glucose between 44 and 58 mg per 100 ml at some time during an oral glucose tolerance test.[2] However, the glucose response of the present patient must be considered in context with the clinical problem. The general pattern of the oral glucose tolerance test was abnormal, with initial hyperglycemia (200 mg per 100 ml in the first half hour) and a relatively rapid fall in plasma glucose to 52 mg per 100 ml by three hours. As continuous monitoring was unavailable, we cannot ascertain the exact minimal level to which plasma glucose may have fallen in this patient. The development of her chief complaint, headache, at the time of the lowest measured plasma sugar level and her own observation that food often relieved her headaches were additional points suggesting an etiological relationship between symptoms and blood glucose levels.

The pattern of response to the oral glucose tolerance test is a great help in classifying patients with hypoglycemia.[3] The presence of a "reactive" rather than a "fasting" hypoglycemia in this patient makes it unlikely that the diagnosis is the result either of autonomous production of insulin by an insulinoma or of heterogenous factors involved in the hypoglycemia related to nonpancreatic tumors.

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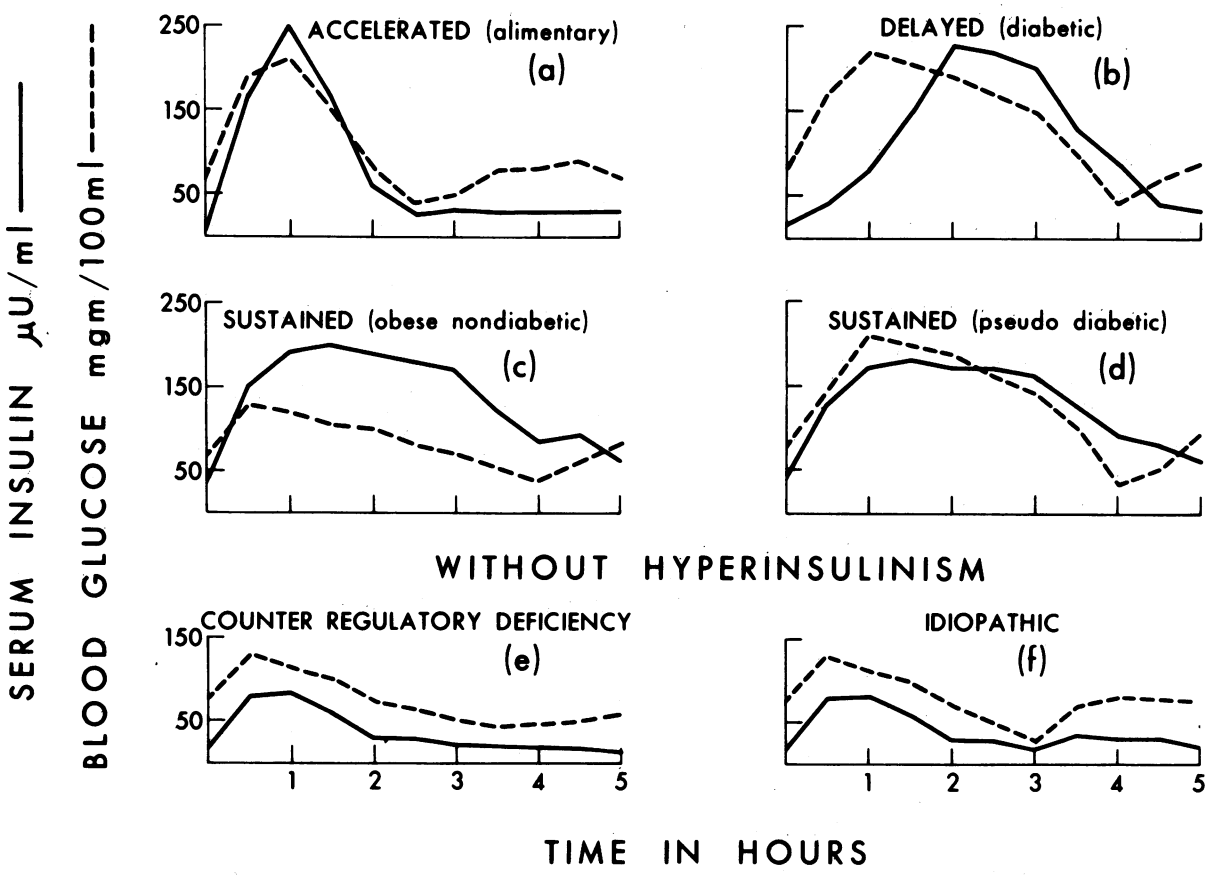

Chart 1.—Patterns of Reactive Hypoglycemia: Reactive hypoglycemia with reactive hyperinsulinism (a,b,c,d). Reactive hypoglycemia with normal insulin response (e,f). The abscissa records time after ingestion of 100 gm of glucose.

Classification of Reactive Hypoglycemia

With the establishment of a "reactive" type of hypoglycemia by clinical history, as well as by plasma glucose measurements, it is then useful to determine whether the pattern of response to the oral glucose load is one of "early" or "late" hypoglycemia. A typical "early" hypoglycemia occurs within three hours of the ingestion of glucose, whereas "late" hypoglycemia occurs three to five hours after receiving the glucose. The pathogenetic mechanisms and management of these responses are quite different.

TABLE 1.—*Classification of Reactive Hypoglycemia*

"Early" Hypoglycemia
Postgastrectomy
Increased vagal tone
"Late" Hypoglycemia
Diabetic reactive hypoglycemia
Nondiabetic "late" hypoglycemia
Obesity
Pseudodiabetes
Counter regulatory deficiency
Idiopathic reactive hypoglycemia

"Early" Hypoglycemia. The present patient demonstrated a pattern of glucose response in the first hour that is characteristic of the alimentary type (Chart 1,a). There was an exaggerated rise of the ascending limb of the curve to reach supranormal values within 30 minutes, followed by a rapid descent associated with symptoms. Although serum insulin levels were not measured in this patient, they almost invariably reach very high levels in the first hour when associated with this particular type of plasma glucose response. "Early" hypoglycemia is quite common in postgastrectomy cases[4] but may also occur in other patients, especially in thin, nervous, compulsive,

hyperactive persons who often complain of gastrointestinal difficulties compatible with increased vagal tone.

The pathogenesis of this pattern of response consists of at least two components: accelerated rate of glucose absorption and intestinal betacytotropic factors.

Accelerated Glucose Absorption. The most obvious cause of accelerated glucose absorption is an abnormally rapid absorption of the alimentary glucose in patients who have had gastrectomy, as well as in those who simply have accelerated gastric emptying, possibly owing to increased vagal tone. Hyperinsulinism, resulting from the initial hyperglycemia, as well as from the increased vagal effect on pancreatic beta cell secretion, produces hypoglycemia.

Intestinal Betacytotropic Factors. It has been clearly demonstrated that the hyperinsulinism which is observed in patients who have had gastrectomy cannot be the result of only the accelerated rate of glucose absorption, since similar hyperinsulinism does not develop when glucose is infused rapidly to produce comparable levels of hyperglycemia.[4] This finding, that the insulin response depends on the route of glucose administration rather than on the circulating glucose level alone, was a very exciting development in the understanding of insulin secretion and its control. It had long been known that a given amount of glucose produced higher blood glucose levels when administered intravenously than when ingested. The assumption was that when glucose was administered orally the time necessary for gastrointestinal absorption and removal by the liver before reaching the systemic circulation accounted for the lower levels. If this were the case, then the higher glucose concentration in the pancreatic artery after intravenous administration would have been expected to produce higher levels of circulating insulin than did glucose by mouth. However, when techniques were developed to measure insulin, it was surprisingly reported that oral glucose produced much higher insulin levels than did comparable intravenous doses.[5] This finding suggested that insulin release was not dependent on blood glucose levels alone and that something produced during alimentation was enhancing the stimulatory effect of glucose on insulin release.

Table 2 relates the historical sequence[5] in the development of the concept that betacytotropic factors are present in normal subjects. In 1904 it was reported that secretin administration produced beta cell hyperplasia. This finding was overlooked until after the discovery of insulin, at which time it was reported that secretin also reduced the blood glucose of dogs. However, when improved micromethods were developed for measuring blood glucose, it was observed and subsequently confirmed that there was no real hypoglycemic effect of secretin in dogs.[5] Thus, for a time the concept of a role of secretin as a betacytotropic substance was discarded. Only after insulin measurements demonstrated the superior insulinotropic effect of oral as compared with intravenous glucose was the problem reinvestigated.

TABLE 2.—*Historical Sequence of Development[5] of Concept that Betacytotropic Factors Are Present in Normal Persons*

1904	Secretin Induced B-Cell Hyperplasia
1923	Secretin Reduced Blood Sugar in Dogs
1940	Hypoglycemic Effect of Secretin Not Confirmed
1964	Oral Glucose Increases Insulin Levels More Than IV Glucose
1966	Extracts of Duodenum Increased Blood Insulin Level, as did the following:
	Secretin
	Pancreozymin
	Gastrin
	Glucagon-Like Substance

When extracted duodenal mucosa was shown to stimulate insulin release[6] the term "gut factor" became widely used, and its chemical isolation, purification, and characterization were expected momentarily. The early reports of secretin-induced beta cell hyperplasia seemed to be vindicated when secretin was shown to stimulate insulin secretion both *in vivo* and *in vitro,* despite its verified lack of hypoglycemic effect in animals. However, investigators were dismayed when instead of finding a single betacytotropic factor, they found that just about every gastrointestinal hormone tested had insulinotropic properties.[7] Unger[8] reported finding a variety of different peptides with glucagon-like immunoreactivity in gastrointestinal mucosa; these peptides can enhance insulin release. Other known insulin secretogogues found in gostrointestinal mucosa include gastrin and cholecystokinin-pancreozymin.[7] The question of the nature of this gut factor is still unresolved. It is not clear whether all of these enteric hormones participate in the enhancement of insulin release by some common mechanism such as cyclic-AMP (Adenosine 3′ 5′ monophosphate) generation, or whether, as Creutzfeld[7]

speculates, the available data represents pharmacological observations; and the actual physiological betacytotropic hormone remains as yet undetected.

Regardless of its nature, an enteric insulinotropic factor certainly seems to exist and may well be produced excessively in postgastrectomy patients and other persons in whom gastric contents empty at an accelerated rate. An increase in glucagon-like immunoreactivity after oral glucose has been reported recently in two patients with reactive hypoglycemia and has been suggested as a pathogenetic factor in their hypoglycemia.[9]

"Late" Hypoglycemia. Diabetic reactive hypoglycemia (Chart 1,b) was first described in 1956 by Seltzer et al[10] in a classic study of 110 patients with normal fasting blood sugar but impaired carbohydrate tolerance. Hyperglycemia persisted for as long as two to three hours after ingestion of glucose, but then was followed by a transient fall to hypoglycemic levels between the third and fifth hour.

In contrast to hyperactive patients with "early" hypoglycemia, patients with "late" hypoglycemia tend to be more phlegmatic, with a high incidence of obesity, and frequently have a positive family history of diabetes mellitus. Serum insulin response to glucose is delayed initially in patients with early adult-onset diabetes, accounting for their carbohydrate intolerance, but gradually rises so that by the second and third hour of the glucose tolerance test hyperinsulinism occurs.[11] Thus, the pathogenesis of this type of "late" hypoglycemia is believed to be within the beta cell itself, and it is thought to represent one of the earlier manifestations of diabetes mellitus.

Nondiabetic "late" hypoglycemia has been described in obese patients who have an early and sustained release of insulin in association with peripheral insulin antagonism (Chart 1,c). This peripheral antagonism has been variously ascribed to abnormally enlarged adipose cells, intramuscular inhibition of glucose metabolism by raised fatty acids, or a combination of these and other, as yet unknown, antagonists. Whatever the cause, this peripheral antagonism to insulin's action results in a delayed postprandial clearance of circulating glucose, although an abnormal elevation of blood glucose does not occur. The prolongation of glucose clearance may stimulate the beta cells and, in addition to the excessive ingestion of calories with their consequent release of betacytropic factors, contribute to the well-documented islet cell hyperplasia and sustained hyperinsulinism found in most obese persons.[12] When islet cell hyperplasia progresses so that the postprandial hyperinsulinism overcompensates for the peripheral antagonism, "late" hypoglycemia occurs.

Nondiabetic "late" hypoglycemia has also been described in patients who have been referred to as having pseudodiabetes (Chart 1,d). These patients have an early and sustained hypersecretion of insulin in association with both an abnormal elevation and a delayed clearance of glucose. In these patients mild carbohydrate intolerance occurs during the initial two or three hours of a glucose tolerance test, and then a "late" hypoglycemia occurs at four or five hours. The presence of a normal or, more often, a supranormal early phase of insulin release differentiates these patients from those with "true" diabetes mellitus. In pseudodiabetes an early release of insulin occurs in response to glucose ingestion. An end organ resistance to the action of these high levels of circulating insulin, however, provides the best explanation for the abnormally elevated blood glucose levels during the first hour of the glucose tolerance test.

In a series of 238 obese subjects reported upon by Faludi et al,[13] 101 had "late" hypoglycemia four hours after a glucose tolerance test. Of these, 27 had normal carbohydrate tolerance in the first three hours, while 74 showed minimal hyperglycemia during this time. Although measurement of early insulin release was not reported in this study, it is our experience that the majority of obese subjects with normal fasting blood glucose and only minimally impaired carbohydrate intolerance would have a supranormal initial release of insulin after glucose and could be termed as having "pseudodiabetes."[12]

Certain regulatory mechanisms are normally available to counteract any excessive hypoglycemic effect of insulin during the latter part of a glucose tolerance test (Chart 1,e). These include pancreatic glucagon, catecholamines, growth hormone, sympathetic nervous stimulation, and cortisol. Deficiency in release of these substances in response to hypoglycemia may thus lead to more pronounced and sustained hypoglycemia.

In the presence of normal glucose tolerance and normal insulin release over the first two hours, patients with reactive hypoglycemia should

first of all be carefully evaluated for deficiencies, of the counter regulators. In the absence of these deficiencies, such cases have been classified as idiopathic reactive hypoglycemia (Figure 1,f).

Diagnosis and Treatment of Reactive Hypoglycemia

In patients without fasting hypoglycemia who have vague autonomic symptoms temporally related to meals, diagnosis is best established by a five-hour oral glucose tolerance test. This test is preferably supervised by a physician so that, in addition to regular blood sampling every 30 minutes, he can obtain a blood sugar determination at the first sign of symptoms, lest a transient period of hypoglycemia be missed.

Treatment is based on the pattern of reactive hypoglycemia obtained. The measurement of serum insulin and blood sugar better delineates the physiological disturbance as shown in Chart 1. In our laboratory, fasting levels of insulin seldom are above 30 μU per ml in normal persons but may be as high as 50 μU per ml in obese persons. After a glucose load, the normal person usually does not have an increase in serum insulin level above 100 μU per ml during his peak insulin response between 30 and 60 minutes.

In an accelerated hyperinsulinism with early hypoglycemia (Chart 1,a) treatment is aimed at reducing the large quantity of food suddenly being presented to the small intestine after meals in patients who have had gastrectomy or those with increased vagal tone, in order to reduce rapid excursions of blood glucose. The patient is offered small, frequent, high protein feedings which contain no processed sugar and only limited carbohydrate. Anti-cholinergic drugs have also been used to inhibit vagal tone and delay gastric emptying. In a well studied case, such cholinergic blockade reduced the rate of gastric emptying, normalized the exaggerated hyperinsulinism and corrected the "early" hypoglycemia.[14] Certain pharmacological agents, including diazoxide,[14] mannoheptulose,[15] and diphenylhydantoin sodium (Dilantin®),[16] may induce hyperglycemia in man with a reduction in serum insulin levels. While these agents offer possible therapeutic approaches in this and other types of reactive hypoglycemia, they as yet have not received adequate clinical trials.

Delayed hyperinsulinism with "late" hypoglycemia (Chart 1,b) is the pattern of reactive hypoglycemia found in patients with diabetes mellitus. Elimination of sugar-containing foods and frequent feedings with increased proteins reduces the initial hyperglycemia that precipitates the delayed hyperinsulinism. Also, in this situation restoring the early phase of insulin release with tolbutamide[17] administration has been reported to be clinically useful.[18]

In sustained hyperinsulinism associated with obesity and pseudodiabetes (Chart 1,c and d) caloric intake is lowered to reduce the obesity and interrupt the cycle producing islet cell hyperplasia and consequent hyperinsulinism. Small, spaced feedings low in carbohydrate, free of sugar and increased in protein are also beneficial. In addition, phenformin hydrochloride (DBI®) has proved to be effective in a large group of obese patients by abolishing late hypoglycemia following a glucose load.[13] The mechanism of action involved with the administration of phenformin may be a reduction in the rate of absorption of ingested glucose by the intestinal mucosa, which results in a smaller elevation of blood glucose and consequently decreased insulin production by the hyperplastic pancreatic beta cells.

Specific replacement therapy is difficult in most counter regulatory deficiencies, except in the case of cortisol insufficiency. Thus, reliance on multiple, small, spaced feedings to minimize increases in blood sugar and insulin secretion would be recommended for these patients as well as for those with idiopathic reactive hypoglycemia.

It is of interest that most patients in all the categories of reactive hypoglycemia seem to respond to a substitution of protein for carbohydrate in their diet even though protein ingestion results in insulin release. It has been suggested that the concomitant production of glucagon offsets the action of this insulin.[19]

In summary, the patient discussed today, who is not obese, has a glucose pattern suggestive of alimentary hypoglycemia with an exaggerated early rise and then a return to normal and finally hypoglycemic levels. The Orthonovum® therapy may have produced just enough insulin antagonism to slightly delay the hypoglycemia in this patient from the 120 to 150 minutes normally seen in the more classical cases of alimentary hypoglycemia. Unfortunately, insulin measurements were not undertaken to confirm the impression of accel-

erated hyperinsulinism. Her clinical picture is, however, typical enough to suggest a trial of low carbohydrate, high protein diet of small, spaced feedings. Since the hypoglycemia and symptoms are rather mild, this therapy should be adequate, with anticholinergic agents kept in reserve in case symptoms become more severe. Phenformin might also be of use in alimentary hypoglycemia, since it reduces the rate of glucose absorption.

DR. HAVEL:* How frequently do atypical symptoms, such as headache, occur? Since the glucose tolerance test alone is not very reliable as a diagnostic aid, and not everybody can measure insulin levels, how much do you rely on the history in evaluating the nature of the disorder?

DR. KARAM: This question is difficult to answer. As physicians we were taught that if a person's blood sugar drops from a high level to a low level, we could expect certain autonomic symptoms attributed to epinephrine. In *Body, Mind, and Sugar*, the authors describe the usual responses, but claim that many atypical symptoms can also occur. They describe, for instance, the pitcher in the baseball game who had perfect control until the eighth inning, when he suddenly blew up and walked everybody. They also imply that most husbands who argue with their wives before suppertime are "hypoglycemic," and if only their eating habits were altered their marriage would be blissful. Without documentation of blood glucose levels, it is hard to prove (or disprove) whether these are symptoms of hypoglycemia. However, I would say that I believe atypical symptoms, such as headache, can occur; but I do not know how I could be certain. I suppose we should give the patient the benefit of the doubt if we observe atypical symptoms which occur during documented reactive hypoglycemia and are relieved by eating.

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TRADE AND GENERIC NAMES OF DRUGS

Librium® ..... chlordiazepoxide hydrochloride
Orthonovum® ..... norethindrane with mestranol
Dilantin® ..... diphenylhydantoin sodium
DBI® ..... phenformin hydrochloride

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